08/808261

EP1201

#3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Mesens *et al.*
Appl. No. To be assigned
(Continuation of 08/154,403)
Filed: Herewith
For: **Microencapsulated 3-Piperidynyl-Substituted 1,2-Benzisoxazoles and 1,2-Benzisothiazoles**

Art Unit: To be assigned
Examiner: To be assigned

Atty. Docket: 1611.0510002/AGR

Petition to Make Special Under 37 C.F.R. § 1.102(d) and Incorporated Information Disclosure Statement

JUN 23 1997
RECEIVED

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is a petition to the Assistant Commissioner to make the present patent application as identified above special. The grounds and conditions for granting this application special status are found in M.P.E.P. § 708.02 VIII entitled "Special Examining Procedure for Certain New Applications - Accelerated Examination." The Petition Fee required pursuant to 37 C.F.R. § 1.17 is enclosed.

As provided for in M.P.E.P. § 708.02 VIII, Applicants agree to the special examining procedure detailed therein. In support of this Petition, Applicants provide a discussion of each of the following:

I. The results of a pre-examination search that was made in connection with the present invention;

II. A list of the documents found upon search deemed most closely related to the subject matter encompassed by the claims;

III. A detailed discussion of the documents, which discussion points out, with the particularity required by 37 C.F.R. §§ 1.111(b) and (c), how the claimed subject matter is distinguishable over the documents;

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IV. The claims are directed to a single invention;

V. Additional comments; and

VI. Conclusion.

I. Scope and Results of a Pre-examination Search

The subject matter of the present application relates to sustained-release microparticles comprising a 1,2 benzazole within a polymeric matrix. One sustained-release microparticle can be produced by including risperidone in the form of crystals into a biodegradable and biocompatible polymer, such as poly(lactic) acid, poly(glycolic) acid, and the copolymers of the foregoing. The sustained-release microparticles can be formulated in a liquid injection vehicle for administration to animals suffering from mental illness.

The present application is a continuation application filed herewith. As such, Applicants have not received an Office Action concerning the examination of the present application.

To determine the patentability of the present claims of the application, a thorough and careful keyword computer database search was conducted by Andrea Kamage, a legal assistant of Sterne, Kessler, Goldstein and Fox P.L.L.C. using the DIALOG® database. The keywords selected were sufficient to limit the scope of the search.

The BIOSIS® file was searched using the following word combinations (and permutations thereof):

microparticle; microencapsulate; microsphere; encapsulate

benzazole; antipsychotic; risperidone; 9-hydroxyrisperidone

File 399 (CA SEARCH®: Chemical Abstracts®) was searched using the CAS registry number for risperidone and for 9-hydroxyrisperidone.

Derwent World Patent Index files (350/351) and File 652 (U.S. patents full text) were searched using risperidone and permutations thereof.

Additionally, the results of a prior (June 1996) computer database search, conducted by Judith U. Kim of Sterne, Kessler, Goldstein & Fox P.L.L.C. using the DIALOG® database, were reviewed. In this prior computer database search, the BIOCHEM, BIOTECH, CHEMLIT, PHARM, and 265 (Federal Research in Progress-abridged) DIALOG® files were searched using the following word combinations (and permutations thereof):

microparticle; microencapsulate; microsphere; microgranule;
microbubble; microdroplet
biodegradable; biocompatible
release;
agent; medicament; pharmaceutical; drug
solvent; carrier; emulsion; blend, dispersion; vehicle
wash; extract; remove.

This prior search also included a search of Derwent World Patent Index files (350/351) using the following word combinations (and permutations thereof):

microparticle; microencapsulate; microsphere; microgranule; microbubble;
microdroplet, microglobule; microcapsule; nanosphere
release; agent; medicament; pharmaceutical; drug
solvent; carrier; emulsion; blend; dispersion; vehicle; miscible; nonmiscible;
wash; extract; remove;
biodegradable; biocompatible; bioadhesive; bioerode; polymer; binder.

II. List of Documents Uncovered by the Pre-examination Search

In support of this Petition to Make Special, submitted herewith on Form PTO-1449 is a listing of documents known to the Applicants and/or their attorney and deemed most closely related to the subject matter encompassed by the claims of the present application. This listing of documents is also in compliance with the requirements of 37 C.F.R. § 1.56. Copies of the documents are submitted herewith.

Applicants reserve the right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered.

The Examiner is also referred to the following list of co-pending patent applications:
Appl. No. 08/154,403, filed 11/19/93 (Atty. Docket: 1611.0510000);
Appl. No. 08/725,439, filed 10/03/96 (Atty. Docket: 1611.0530003);
Appl. No. 08/729,277, filed 10/10/96 (Atty. Docket: 1611.0530004); and
Appl. No. 08/403,432, filed 03/14/95 (Atty. Docket: 1611.0510001).

It is respectfully requested that the Examiner initial and return a copy of the enclosed PTO-1449 and indicate in the official file wrapper of this patent application that the documents have been considered.

The pre-examination search uncovered the following documents:

AA1	U.S. Patent No. 3,773,919
AB1	U.S. Patent No. 4,342,870
AC1	U.S. Patent No. 4,389,330
AD1	U.S. Patent No. 4,458,076
AE1	U.S. Patent No. 4,804,663
AF1	U.S. Patent No. 4,883,666
AG1	U.S. Patent No. 4,940,588
AH1	U.S. Patent No. 4,994,281
AI1	U.S. Patent No. 5,008,114
AJ1	U.S. Patent No. 5,158,952

AK1	U.S. Patent No. 5,407,609
AA2	U.S. Patent No. 5,453,425
AB2	U.S. Patent No. 5,478,564

Other Information and Publications

AL1	0 368388	(Europe)
AM1	WO 90/13361	(WIPO)
AN1	WO 94/25460	(WIPO)
AO1	WO 95/13799	(WIPO)

AR1 Megens, A.A.H.P. *et al.*, "Comparative Pharmacology of Risperidone, Its Major Metabolite R 76 477$^{(+,-)}$ and the Corresponding Enantiomers R 78 543 $^{(+)}$ and R 78 544$^{(-)}$ in Rats and Dogs", Janssen Research Foundation, Beerse Belgium, N74694, *Preclinical Research Report* R 64 766/23 (June 1990).

AS1 Megens, A.A.H.P., *et al.*, "*In Vivo* Pharmacological Profile of 9-Hydroxyrisperidone, the Major Metabolite of the Novel Antipsychotic Risperidone: Comparison With Risperidone and Haloperidol", Janssen Research Foundation, Beerse, Belgium, N 96295, *Preclinical Research Report* R 64 766/R76 477 (May 1993).

AT1 Suzuki, K., *et al.*, "Microencapsulation and Dissolution Properties of a Neuroleptic in a Biodegradable Polymer, Poly(d,l-lactide)", *Journal of Pharmaceutical Sciences, Vol. 74*, No. 1, 21-24 (January 1985).

AR2 Ramtoola, Z., *et al.*, "Release Kinetics of Fluphenazine from Biodegradable Microspheres", *Journal of Microencapsulation, Vol. 8*, No. 4, 415-423 (1992).

AS2 Chang, R., *et al.*, "Dissolution Characteristics of Polycaprolactone-Polylactide Microspheres of Chlorpromazine", *Drug Development and Industrial Pharmacy, Vol. 12*, No. 14, 2355-2380 (1986).

AT2 Maulding, H.V., *et al.*, "Biodegradable Microcapsules: Acceleration of Polymeric Excipient Hydrolytic Rate By Incorporation of a Basic Medicament", *Journal of Controlled Release, 3*: 103-117 (1986).

AR3 Leysen, J.E., *et al.*, "Biochemical Profile of Risperidone, a New Antipsychotic", *The Journal of Pharmacology and Experimental Therapeutics, Vol. 247*, No. 2, 661-670 (1988).

AS3 Janssen, P.A.J., *et al.*, "Pharmacology of Risperidone (R 64 766), a New Antipsychotic With Serotonin - S_2 and Dopamine - D_2 Antagonistic Properties", *The Journal of Pharmacology and Experimental Therapeutics, Vol. 244*, No. 2, 685-693 (1988).

AT3 Chouinard, G., *et al.*, "A Canadian Multicenter Placebo-Controlled Study of Fixed Doses of Risperidone and Haloperidol in the Treatment of Chronic Schizophrenic Patients", *Journal of Clinical Psychopharmacology, Vol. 13*, No. 1, 25-40 (1993).

III. Detailed Discussion of the Documents

The documents uncovered by the pre-examination search are discussed below.

Document AA1 describes drug compounds that may be coated, embedded, or intimately mixed in or with a matrix of one or a combination of different chain-length biodegradable polylactide polymers to give a drug-polymer mixture that will provide a controlled sustained release of the drug compound over a period of eight hours to two months or longer. Coating the discrete drug particles can be accomplished by suspending drug particles, granules or pellets (.1 to 2000 microns diameter) in a solvent system in which the drug is not soluble, and which contains in solution the polylactide or polylactide mixture. An agent incompatible with the

polymer-solvent system is added, such as an incompatible polymer, a non-solvent for the polymer, or a salt. The polymer then precipitates, coating the drug particles, granules or pellets. Suitable classes of drugs include antipsychotic agents that affect the central nervous system, such as chlorpromazine and molindone.

Document AB1 describes 3-(1-piperidinylalkyl)-4H-pyrido[1,2-a]pyrimidin-4-one derivatives that are potent serotonin-antagonists.

Document AC1 describes the preparation of microparticles containing an active agent, that may be a psychotherapeutic agent. The method comprises: (a) dissolving or dispersing an active agent in a solvent and dissolving a wall forming material in that solvent; (b) dispersing the solvent containing the active agent and wall forming material in a continuous-phase processing medium; (c) evaporating a portion of the solvent from the dispersion of step (b), thereby forming microparticles containing the active agent in the suspension; and (d) extracting the remainder of the solvent from the microparticles.

Document AD1 describes 3-piperidinyl-1,2-benzisoxazoles and 3-piperidinyl-1,2-benzisothiazoles having antipsychotic and analgesic properties.

Document AE1 describes 3-piperidinyl-1,2-benzisothiazoles and 3-piperidinyl-1,2-benzisoxazoles and their pharmaceutically acceptable acid addition salts that have antipsychotic properties and that are useful in the treatment of a variety of complaints in which serotonin release is of predominant importance. In particular, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one ("Risperidone") is disclosed.

Document AF1describes a method and composition for treatment of neural disorders. The composition is formed by encapsulation within an implantable biocompatible polymeric device of one or more compounds that have the effect of replacing or stimulating functions of the nervous system. An essential feature of the composition is linear release, achieved through manipulation of the polymer composition and form.

Document AG1 describes a process for preparing controlled release powders containing discrete microparticles. The process comprises: (a) forming a solution of the polymer or polymers in a solvent; (b) dissolving or dispersing the active ingredient in the polymer solution to form a uniform mixture; and (c) removing the solvent from the mixture to obtain microparticles having an average size of from 0.1 to 125 micrometers. Each of the microparticles is in the form of a micromatrix of an active ingredient uniformly distributed in at least one non-toxic polymer. The microparticles have a predetermined release of active ingredient. The active ingredient can include antipsychotics such as chlorpromazine and haloperidol.

Document AH1 discloses microencapsulation of physiologically active substances in polylactide polymers using a solvent-evaporation process. The physiologically active substances can include chlorpromazine and haloperidol.

Document AI1 discloses the use of solvent evaporation in preparing pharmaceutical compositions with controlled release active substances. Preferred active substances include those of low water-solubility, including anti-hypertensives, anti-anxiety agents, particularly, haloperidol.

Document AJ1 describes 3-piperidinyl-1,2-benzisoxazoles having long-acting antipsychotic properties and which are useful in the treatment of warm-blooded animals suffering from psychotic diseases. In particular, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one ("9-hydroxyrisperidone") is disclosed.

Document AK1 describes a method of microencapsulating an agent to form a microencapsulated product, having the steps of dispersing an effective amount of the agent in a solvent containing a dissolved wall-forming material to form a dispersion, combining the dispersion with an effective amount of a continuous process medium to form an emulsion that contains the process medium and microdroplets having the agent, the solvent and the wall-forming material, and adding rapidly the emulsion to an effective amount of an extraction medium to extract the solvent from the microdroplets to form the microencapsulated product.

Document AA2 describes physiochemically stable aqueous solutions of risperidone for oral administration which do not contain sorbitol.

Document AB2 describes a process for preparing microparticles of the microsphere type of a water-soluble substance and biocompatible and biodegradable polymer, controlling the kinetics of release of the substance. The process uses a third solvent that is both a solvent for the water-soluble substance and is miscible with the solvent for the polymer, ensuring a homogeneous distribution of the active substance in the polymer phase. The miscibility of the third solvent with the aqueous phase contributes to the incorporation process of the active substance into the microsphere.

Document AL1 describes 3-piperidinyl-1,2-benzisoxazoles and the pharmaceutically acceptable acid addition salts thereof, which are useful as antipsychotic agents.

Document AM1 describes a method of microencapsulating an agent to form a microencapsulated product, having the steps of dispersing an effective amount of the agent in a solvent containing a dissolved wall-forming material to form a dispersion, combining the dispersion with an effective amount of a continuous process medium to form an emulsion that contains the process medium and microdroplets having the agent, the solvent and the wall-forming material, and adding rapidly the emulsion to an effective amount of an extraction medium to extract the solvent from the microdroplets to form the microencapsulated product.

Document AN1 describes a compound that is a pamoate acid addition salt of risperidone.

Document AO1 describes a process for preparing biodegradable microparticles comprising a biodegradable polymeric binder and a biologically active agent. A first phase, comprising the active agent and the polymer, and a second phase are pumped through a static mixer into a quench liquid to form microparticles containing the active agent. Preferably, a blend of at least two substantially non-toxic solvents, free of halogenated hydrocarbons, is used to dissolve or disperse the agent and dissolve the polymer.

Document AR1 describes a comparison between risperidone and the major risperidone metabolite and its enantiomers. Risperidone, its major metabolite, and the corresponding enantiomers, are potent antagonists of serotonin, dopamine, and norepinephrine. The compounds are very comparable both in potency, pharmacological profile, and onset and duration of action. Metabolic conversion of risperidone into its major metabolite or its

enantiomers may contribute to the biological activity of risperidone but is not expected to result in additional secondary pharmacological or toxic effects.

Document AS1 describes a comparison between 9-hydroxyrisperidone with risperidone, ritanserin, and haloperidol in a series of pharmacological tests in rats. 9-hydroxyrisperidone and risperidone differed markedly from haloperidol as indicated by: (1) predominant central $5HT_2$ antagonism (comparable to that of ritanserin); (2) high doses for catalepsy; (3) gradual depression of motor activity; (4) inhibition of amphetamine-induced oxygen consumption preceding inhibition of amphetamine agitation; and (5) pronounced behavioral disinhibitory effects in amphetaminized rats. As the metabolic conversion of risperidone to 9-hydroxyrisperidone does apparently not result in any marked change in activity profile, its major consequence seems to be a prolongation of duration of action.

Document AT1 describes a process of encapsulation of chlorpromazine in polylactide polymers using an emulsification-solvent evaporation method. When drug loading was less than or equal to 18 percent, the drug was in the form of a solid solution in microspheres of polylactide. At higher drug loadings, crystalline drug was present. The drug release rate decreased as microcapsule size increased. Document AT1 reports that release characteristics of the polylactide microspheres can be modified by at least three methods: (a) by employing polymers of different molecular weights; (b) by changing the particle size of the microsphere; and (c) by controlling the drug loading to contain different proportions of crystalline drug and drug in solid solution.

Document AR2 describes release kinetics of fluphenazine-loaded microspheres prepared using biodegradable lactide and lactide-co-glycolide polymers. Sustained release of fluphenazine was achieved with fluphenazine-loadings of up to 30 percent in both the lactide and lactide-co-glycolide polymers. The release profiles showed a "lag" period followed by an accelerating release phase and in some cases a decay period, *i.e.*, the release profiles were sigmoidal. Document AR2 reports that polymer degradation, the primary rate-determining step controlling drug release occurred by a mechanism involving propagation of active sites, drug release reflecting the spread of this degradation throughout the polymer.

Document AS2 reports on studies conducted on the preparation of controlled release polycaprolactone-polylactide microcapsules of chlorpromazine, and on release of the drug from the microcapsules in pH 7.0 buffer medium. Chlorpromazine was released from the microspheres in a biphasic manner consisting of an initial fast release phase followed by a slow release phase. Increasing the drug content increased the initial drug release rate, but no significant drug loading effect on the second stage dissolution rate was noted. There was no significant effect of particle size on the drug release from the microspheres.

Document AT2 describes acceleration of a polymeric excipient hydrolytic rate by incorporation of a basic medicament. Thioridazine HCl was incorporated into microspheres of poly(D, L-lactide) with an almost immediate release occurring both *in vitro* and *in vivo*. When the less soluble thioridazine base was incorporated into the microspheres, the drug was released *in vivo* over a few days. This is contrary to the results expected with a polymer such as poly(D, L-lactide) which degrades in about one year and releases drugs over weeks to months.

Document AR3 reports on the biochemical profile of risperidone. Studies of the clinical, pharmacological, and biochemical properties of risperidone, in comparison with ritanserin and haloperidol, suggest that the predominant, potent 5-HT blocking activity, combined with potent DA receptor blockade, may underlie the improved therapeutic activity of risperidone. The *in vitro* biochemical properties of risperidone are in agreement with the reported *in vivo* pharmacological profile, and the relation to clinical findings is discussed in document AR3.

Document AS3 reports on comparative studies of risperidone with ritanserin and haloperidol. Because risperidone is a dopamine-D_2 antagonist, antidelusional, antihallucinatory, and antimanic actions are expected. The first clinical studies indicate that two additional therapeutic targets, which are not reached with classical neuroleptics, may be obtained with risperidone in the monotherapy of schizophrenia and related disorders: very important contact and mood elevating properties; and extrapyramidal symptoms-free maintenance therapy.

Document AT3 reports on the result of a placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. The results of the study suggest that risperidone, at the optimal therapeutic dose of 6mg/day, produces significant improvement in both positive and negative symptoms without an increase in drug-induced parkinsonian symptoms, and with a significant benefical effect on tardive dyskinesia.

IV. The Claims are Directed to a Single Invention

The present application includes claims 28-30. Applicants respectfully submit that claims 28-30 are directed to a single invention.

V. Additional Comments

Contrary to the teachings of the above-listed patents and other information, the present invention as claimed is directed to novel sustained-release microparticles. The above-listed patents and other information do not teach or suggest microparticles that contain risperidone, or a pharmaceutically acceptable acid addition salt thereof, in crystalline form and a biodegradable and biocompatible polymeric matrix. The above-listed patents and other information do not teach or suggest sustained-release microparticles produced by including risperidone, or a pharmaceutically acceptable acid addition salt thereof, in the form of crystals into a biodegradable and biocompatible polymer selected from the group consisting of poly(lactic) acid, poly(glycolic) acid, copolymers of the foregoing, and polyorthoesters. Applicants respectfully submit that the claimed invention is not taught or suggested by any of the above-listed documents taken alone or in combination.

VI. Conclusion

This statement should not be construed as a representation that more material information does not exist.

In accordance with the requirements of 37 C.F.R. § 1.102(d), Applicants submit herewith the Petition Fee of $130.00 as required by 37 C.F.R. § 1.17. The petition fee is included in attached SKG&F Check No. 18705.

Applicants respectfully submit that all of the requirements of 37 C.F.R. § 1.102 and M.P.E.P. § 708.02 have been met in order to place the present application in special status. It is therefore respectfully requested that this Petition be granted.

Respectfully submitted,

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